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Article

Development and characterization of PLGA-Bupivacaine and PLGA-S75:R25 Bupivacaine (Novabupi®) biodegradable implants for postoperative pain

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In the hospital environment, postoperative pain is a common occurrence that impairs patient recovery and rehabilitation and lengthens hospitalization time. Racemic bupivacaine hydrochloride (CBV) and Novabupi® (NBV) (S (-) 75% R (+) 25% bupivacaine hydrochloride) are two examples of local anesthetics used in pain management, the latter being an alternative with less deleterious effects. In the present study, biodegradable implants were developed using Poly(L-lactide-co-glycolide) through a hot molding technique, evaluating their physicochemical properties and their *in vitro* drug release. Different proportions of drugs and polymer were tested, and the proportion of 25%:75% was the most stable for molding the implants. Thermal and spectrometric analyses were performed, and they revealed no unwanted chemical interactions between drugs and polymer. They also confirmed that heating and freeze-drying used for manufacturing did not interfere with stability. The *in vitro* release results revealed drugs sustained release, reaching 64% for NBV-PLGA and 52% for CBV-PLGA up to 30 days. The drug release mechanism was confirmed by microscopy, which involved pores formation and polymeric erosion, visualized in the first 72 h of the *in vitro* release test. These findings suggest that the developed implants are interesting alternatives to control postoperative pain efficiently.

Keywords: Postoperative Pain. Bupivacaine. Novabupi®. Biodegradable Implants. PLGA. Drug Delivery.

INTRODUCTION

Pain is characterized as an unpleasant experience, which may be of a sensory or emotional nature, and which is or is not associated with tissue damage by the International Association for the Study of Pain (IASP). In the postoperative context, pain is one of the most common occurrences in patients in the hospital environment. Couceiro et al., (2009) estimated that severe or moderate postoperative pain affects about 40 to 60% of patients who have undergone extensive surgery. Such a condition impairs patient recovery and rehabilitation and may lead to prolonged hospitalization and, consequently, higher treatment costs (Lamplot *et al.*, 2014).

The strategy for postoperative pain control is to block the generation, transmission, perception, and appreciation

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of nociceptive stimuli, which can be implemented at various levels in the central nervous system and the peripheral nervous system (Wu, Raja, 2011). Thus, the treatment can be based on several pharmacological classes, the main ones being steroidal anti-inflammatory drugs (NSAIDs), opioids, and anesthetics, in the most diverse routes of administration (Elmallah *et al.*, 2018; Zhang *et al.*, 2018). Local anesthetics are widely used drugs that cause temporary loss of pain by inhibiting the transmission of nerve impulses (Pereira *et al.*, 2013).

Bupivacaine Hydrochloride (CBV) belongs to amine-amides local anesthetics introduced in the 60s, widely used in surgical procedures, mainly for prolonged regional blocks thanks to its moderate action, relatively long duration, conduction block, and sensory block to the detriment of the motor; (Nelson *et al.*, 2018). The drug has a chiral carbon in its structure, resulting in two enantiomeric forms: dextrobupivacaine (R (+) bupivacaine) and levobupivacaine (S (-) bupivacaine). However, there are systemic adverse reactions, mainly related to the R (+) isomer, including cardiovascular and neurological events (Hamaji *et al.*, 2013). Hence, Novabupi® (NBV) was launched in the market (75% S (-), 25% R (+) bupivacaine) (Cox *et al.*, 1998), and it represents a safer alternative for local anesthesia.

In an attempt to reduce systemic adverse effects of local anesthetics and improve its clinical profile, efforts are being made to create different delivery forms, such as polymeric implants. Among the advantages of this pharmaceutical form, one can mention the convenience and better acceptance by the patient, improvement in the pharmacokinetic profile of the drug; thus, avoiding high plasma peaks, resulting in fewer adverse effects and greater specificity at the site of action (Wang *et al.*, 2019) . Poly (L-lactide-co-glycolide) (PLGA) is a polymer approved by the Food and Drug Administration (F.D.A.) with excellent biological degradation characteristics, as well as interesting properties for the development of pharmaceutical formulations (Mir *et al.*, 2017).

Currently, there are alternative formulations of bupivacaine approved by the F.D.A. They are EXPAREL®, a drug release lasting 72 h (Weinberg, 2010), and Xaracoll ® (Velanovich *et al.*, 2019), a bupivacaine collagen implant that releases immediately after surgery, up to 96 h, used for post-hernia surgery. Thus, efforts are being made to achieve better and long-lasting formulations.

When considering the pharmaceutical forms already present on the market, recent studies suggest that the liposomal form does not exhibit effectively different efficacy than traditional bupivacaine (Hussain *et al.*, 2021; Alijanipour *et al.*, 2017). Still, it has been suggested that implants have several advantages when compared to other drug delivery systems as (1) they improve the pain control profile, (2) they are easily implanted, and (3) they have a high acceptance (Velanovich *et al.*, 2019; Leiman *et al.*, 2021). Therefore, this study is even more significant for the development of new biodegradable implants with a drug that exhibits a better safety profile (Novabupi®).

To the best of our knowledge, the absence of relevant research developing and comparing anesthetic implants encouraged us to conduct the current study, in which PLGA-based implants for CBV and NBV were developed, given the benefits in prolonging drug delivery and minimizing systemic adverse effects. The materials' physicochemical characteristics and their *in vitro* and drug release mechanisms were evaluated.

MATERIAL AND METHODS

Material

Bupivacaine hydrochloride and Novabupi® were a gift from Cristália Produtos Químicos Farmacêuticos LTDA (São Paulo, Brazil). Poly-lactide-co-glycolide copolymer (PLGA 50:50 Resomer® RG 503 -Evonik Röhm GmbH; Darmstadt, Germany). Methanol and acetonitrile HPLC grade (Merck Brazil, São Paulo, Brazil) were used. Ultrapure water was produced by a Milli-Q System (Millipore, Massachusets, U.S.A.). Other chemicals were of analytical grade.

Biodegradable implants preparation

The mixture of each drug with PLGA was solubilized in a sufficient amount of acetonitrile and ultrapure water under magnetic stirring and at room temperature. The resulting solution was frozen in liquid nitrogen and lyophilized for 24 h (Lyophilizer K105, LIOTOP). After

obtaining homogeneous powder material (CBV-PLGA and NBV-PLGA), implants were molded in a tubular shape, with dimensions of 6 mm in length and approximately 0.45 mm in diameter, measured with the aid of a caliper and trocater, respectively (Accurus® 25), through hot-molding on a Teflon® plate heated to 100 ºC (Francisco *et al.*, 2019).

Different drug/polymer ratios were tested (12.5%, 25%, and 50% drug/polymer) to find the optimized formulation.

Differential scanning calorimetry (DSC)

Roughly 1 mg of each of the following samples was weighed: PLGA; CBV; NBV; CBV-PLGA, and NBV-PLGA lyophilized material (25%:75% drug/polymer ratio). A DTG60 calorimeter (Shimadzu) was used for the analysis, with a heating rate of 10 ºC/min, ranging from room temperature to 300 ºC, with nitrogen's inert atmosphere.

Fourier transform infrared spectroscopy (FTIR)

Samples of drugs, polymer, and lyophilized material (CBV-PLGA and NBV-PLGA) 25%:75% drug/polymer ratio were analyzed in a Nicolet-6700 equipment of the Nuclear Technology Development Center – CDTN (UFMG – Brazil).

Development of the method in high-performance liquid chromatography (HPLC)

An analytical method for both drugs was developed based on Brazilian Pharmacopeia 5th ed. A Poroshell 120 column, reverse phase, with dimensions of 4.6 cm in length, 50 mm in diameter, and particle size of 2.7 µ was used. The mobile phase was composed of a mixture of phosphate buffer and acetonitrile (65:35), 1,25 mL/min, with pH 6.85, acidified with 1M phosphoric acid, with an ultraviolet (U.V.) detector at 263 nm, and oven temperature of 50 ºC.

In vitro drug release test

Each implant was placed in a 2 ml Eppendorf containing PBS pH 7.4, which had the buffer content renewed at predetermined intervals, satisfying the sink conditions. The test was done with six implants of each group (CBV-PLGA and NBV-PLGA), in a TE 424 incubator (TECNAL, Brazil), at a rotation of 30 rpm and temperature of 37 ºC, incubated for 30 days in order to mimic organisms' conditions. Samples were withdrawn at 1, 2, 6, 9, 12, 15, 21, and 30 days, and their evaluation was made by HPLC using the developed methodology.

Scanning electronic microscopy (SEM)

Implants were applied to the *in vitro* drug release test, removed after 24, 48, and 72 h, and analyzed by scanning electronic microscopy (SEM). Prior to microscopic examination, the samples were sputter-coated with a gold layer under an argon atmosphere for 1 min (BALTEC MED020 Coating System, BALTEC AG, Germany). Scanning electron microscopy (SEM) analysis was performed using a FEG-Quanta 200 FEI microscope (F.E.I., U.S.A.) operating at 5 kV. Prior to visualization, implants were washed with distilled water, blotted with wipes to dry off excess water, and then dried for 72 h in a vacuum desiccator at room temperature and magnified by 26x and 5000x.

Statistical analysis

Data are presented as mean ± S.D. The unpaired t-test was used to compare the *in vitro* release test. $P < 0.05$ was considered significant. Statistical analysis was performed using GraphPad Prism 8.4.3.

RESULTS

Biodegradable implants preparation

Initially, the aim of using the different concentrations of drugs (12%, 25%, and 50%) was to determine the highest concentration that would not significantly affect the material's molding properties. A lyophilized mixture containing 12.5% and 25% drug had adequate properties for the molding process, whereas, at a concentration of 50%, the material was friable and difficult to handle. Therefore, it was decided

that the 25% mixture for the implants' development was the highest concentration that displayed good properties in the hot molding process.

The implants were molded into a tube shape from lyophilized material, 6 mm long and approximately 0.45 mm in diameter. The average weight of CBV implants (n = 15) was 1.18 ± 0.13 mg, whereas of NBV implants was 1.2 ± 0.14 mg (Figure 1).

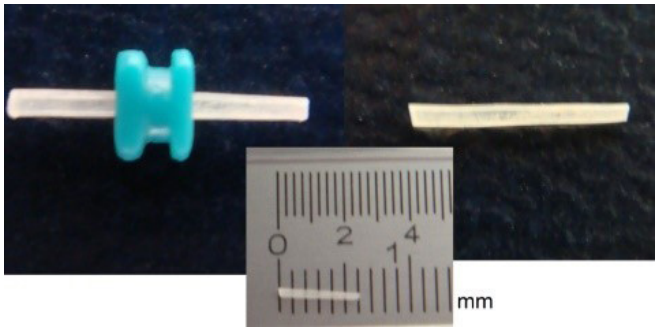

FIGURE 1 - CBV-PLGA implant produced through a hot-molding technique. The implant is compared using a 0.45 mm Trocater and its length with a ruler.

Differential scanning calorimetry (DSC)

Thermal analysis was employed to evaluate possible physical-chemical interactions between drugs and PLGA. The polymer thermogram exhibited an endothermic peak around 52 ºC (Figure 2), which corresponds to its glass transition temperature (Tg), as described in the literature (Jahangiri *et al.*, 2014).

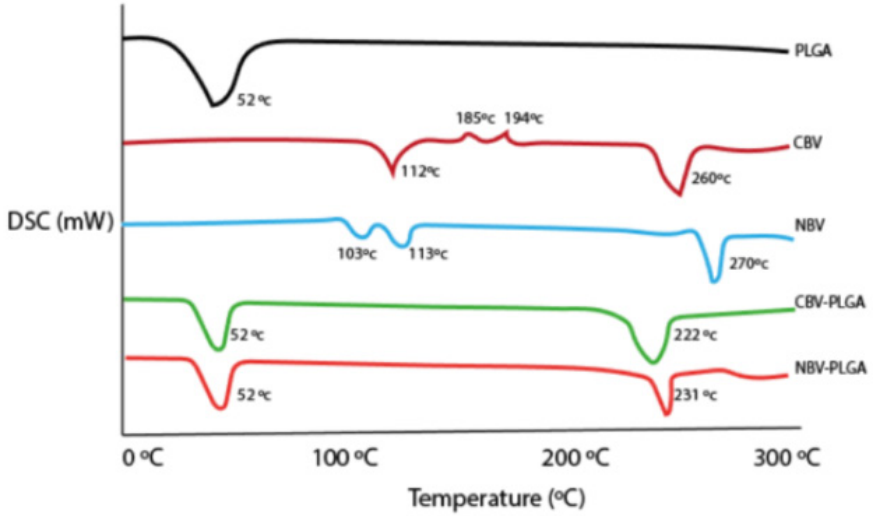

FIGURE 2 - DSC curves for PLGA, CBV, NBV, and lyophilized mixtures of CBV-PLGA and NBV-PLGA. Samples were heated from 0 to 300 ºC.

Regarding CBV, an endothermic event is observed around 112 ºC, probably indicating the molecule's dehydration. Additionally, there are two exothermic events around 180 ºC, which are involved in the transition from the metastable form of the anhydrous drug (Form I) to the stable form (Form II) (Sykuła-Zając *et al.*, 2011). Finally, there is an endothermic event at 260 ºC that represents the melting of CBV, followed by decomposition

of the sample. Moreover, analyzing NBV's thermogram, endothermic events are observed in the region of 90 to 113 ºC, and they are probably also related to the dehydration of the molecule when the sample is heated. Another event at 270 ºC indicated the melting temperature of NBV, followed by decomposition (Figure 2). Therefore, there was no metastable transition for this drug.

Regarding drug/polymer (CBV-PLGA and NBV-PLGA) lyophilized material, an endothermic event is observed around 52 ºC, representing the polymer's Tg. The melting temperature of the drugs was reduced; CBV showed 231 ºC, whereas NBV 222 ºC, with the values of the isolated drugs above 260 ºC, as previously demonstrated (Figure 2).

According to drug/polymer thermal analysis, there was a minor reduction in the drug's melting temperature, which could be explained by the drug's dispersion in the polymeric matrix, forming physical interactions such as hydrogen bonds and/or van der Waals in the formation of a matrix-type delivery system (Anwer *et al.*, 2016). Moreover, no other significant peaks were identified for all formulation components individually (CBV/NBV and PLGA) or the mixtures, supporting that no significant chemical changes or interactions occurred between drug and polymer. Finally, there were no losses due to dehydration in drug/polymer material, suggesting that the lyophilization process efficiently removes water from the material.

Fourier transform infrared spectroscopy (FTIR)

FTIR technique was applied to evaluate the compatibility between drugs (CBV and NBV) and PLGA, comparing the spectroscopical fingerprint of each material (Figure 3). The PLGA FTIR spectrum has demonstrated bands between 3000 and 2900 cm^{-1}, corresponding to the stretching of the C-H bonds of CH_2 and CH_3 groups, and there is an intense absorption band at 1755 cm^{-1}, characteristic of an ester carbonyl C=O stretch. Moreover, bands between 1300 and 1200 cm^{-1}, possibly corresponding to the stretching of the C-O bond, as well as bands between 1500 and 1300 cm^{-1}, that represent the deformation of the C-H bond of CH_2 and CH_3 groups (Lorincz *et al.*, 2015; Sadeghi-avalshahr *et al.*, 2017).

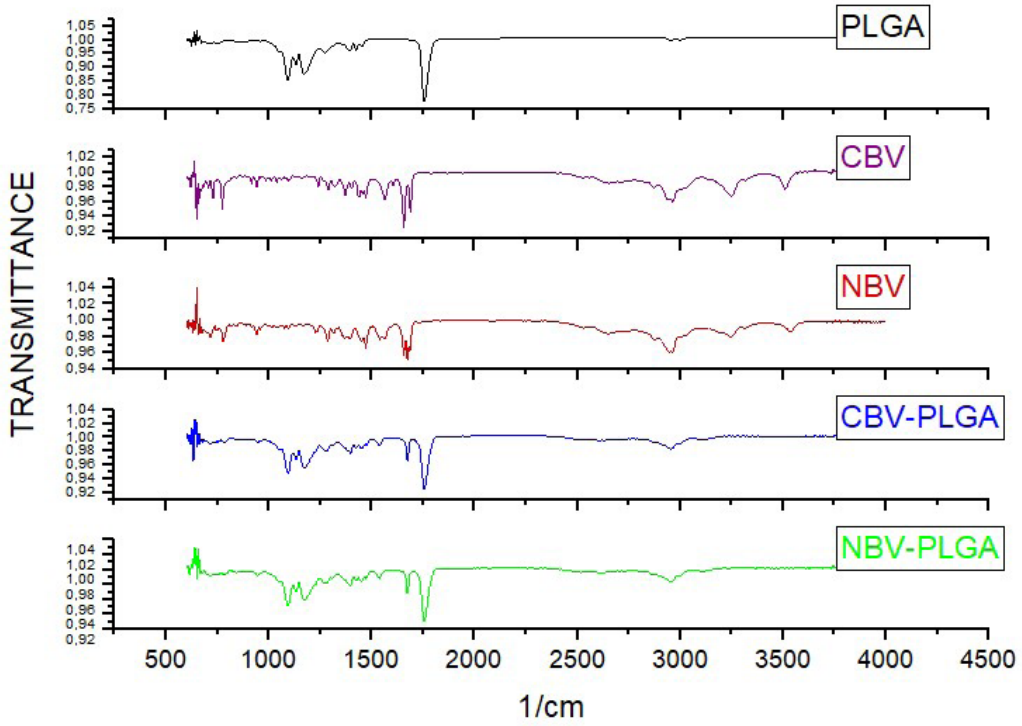

FIGURE 3 - FTIR spectra of PLGA, CBV, NBV, and lyophilized mixtures of CBV-PLGA and NBV-PLGA. The fingerprint of each molecule can be observed through the functional groups. Wavelengths from 400 to 4000 cm^{-1}.

Regarding the drugs (CBV and NBV), bands at 3510 cm^{-1} were observed, related to a quaternary ammonium salt since the molecule is in the form of hydrochloride, and at 3246 cm^{-1} corresponding to a secondary amide N-H stretch. Ranging between 3000 cm^{-1} and 2800 cm^{-1}, some bands represent the stretching of the C-H bond in groups C.H., CH_2, and CH_3. Another relevant point on the drug's spectrum is bands in 1669 cm^{-1} and 1665 cm^{-1}, referring to the stretching of C = O bonds of amides and stretching of C-N groups, respectively (Martins *et al.*, 2017). The existing band at 2954 cm^{-1} is related to the stretching of the C-H bond in aliphatic groups (C.H., CH_2, and CH_3). The lyophilized materials have demonstrated similar bands of the individual components, with minor displacements (Figure 3).

Regarding the spectroscopical analysis, one can state that there is no creation of new bands on lyophilized materials (CBV-PLGA and NBV-PLGA), only the displacements related to the formulation component's functional groups (Soares *et al.*, 2017). The bands' disappearance is related to the N-H stretching of secondary amides and the quaternary ammonium salt present in the CBV and NBV individual spectrums. That is probably due to the lower concentration of the drug in relation to the polymer since the established drug/polymer ratio is 25%:75%. The data presented indicate that the mixture between the drugs and the polymer did not demonstrate any unwanted chemical reactions, which could form other compounds unrelated to the formulation.

In vitro release profile

The cumulative release profile of CBV-PLGA and NBV-PLGA implants was monitored for 30 days (Figure 4). During the initial 24 h, there was a rapid increase in drug release for both implants, 22% and 40%, respectively. On the thirtieth day, the accumulated release percentage comprised 53% for CBV-PLGA and 64% for NBV-PLGA. The release between the two groups was considered different ($p < 0{,}0003$). During the test, the implants showed macroscopical differences through time, demonstrating drug release.

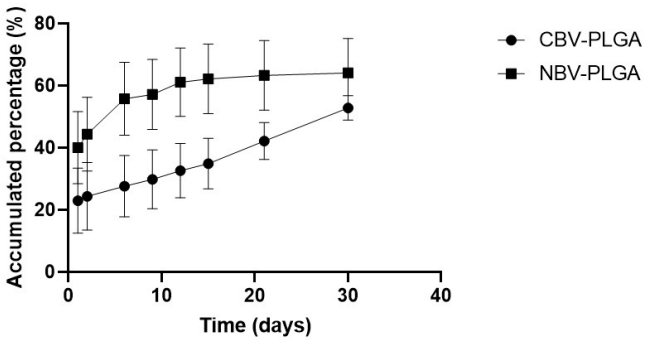

FIGURE 4 - *In vitro* release test of CBV-PLGA (circle) and NBV-PLGA (squares) implants in PBS, pH 7.4, 37ºC. Each studied group had six implants evaluated. Statistical difference was found between the two groups ($p < 0.0003$).

The release of drugs in systems containing the PLGA polymer is zero-order or first-order, divided into three stages. The first stage is called an initial burst, in which the drug is released on the implant surface, resulting in an intense increase in concentration in a short time. In the second stage, the drug diffusion process is initiated through the polymeric matrix to the external environment, mainly governed by the molecule's solubility, in addition to breaks in the polymeric chains through hydrolytic reactions. In the third and last stage, there is an intense erosion of the polymer and, consequently, the release of the drug into the medium (Lee *et al.*, 2010). Therefore, the results obtained conclude that despite some differences, the release profile of both types of implants (CBV-PLGA and NBV-PLGA) follows the same expected release pattern.

Sendil *et al.*, 2003 performed and evaluated the production of biodegradable implants containing bupivacaine, in which the *in vitro* release exhibited a rapid pattern of release of its content, less than five days, which would be too short for postoperative pain. Another study (Kranz *et al.*, 2008) carried out the formulation of implants formed *in situ* to release bupivacaine that resulted in a varied release of 10% to 50%, depending on the medium used, in a period of 48 h. A hydrogel containing PLGA with bupivacaine was made, showing the release for up to 7 days (Taraballi *et al.*, 2014). PLGA-Bupivacaine microparticles were developed, releasing more than 90% of its content up to 35 days, comparable

to a similar drug delivery system containing lidocaine, developed by the same research group (released up to 28 days) (Kim *et al.*, 2019). Novabupi® also has different formulations being studied (Grillo *et al.*, 2010), in which alginate nanoparticles were tested, revealing a slower release when compared to regular Bupivacaine. That agrees with other previous works (Zhang *et al.*, 2008) that revealed a burst release during the first 8 h and more than 90% of drug content in 48h, exhibiting a fairly constant release rate.

Therefore, it is suggested that the developed implants follow the same release pattern as other different PLGA-based systems, with a controlled release over time, and an initial burst effect, suggesting the presence of the drug on the surface of the implants. Moreover, the difference in final concentration between CBV-PLGA and NBV-PLGA implants may have been due to different interactions between the drug and the polymer, considering that there is a difference in the enantiomeric proportion of the drugs (CBV is a racemic mixture, whereas NBV has enantiomeric excess). Further studies are necessary to understand drug/polymer interactions fully.

Scanning electronic microscopy (SEM)

SEM micrographs were acquired to analyze the morphological changes in the implants' surface prior to the *in vitro* release test and after 24, 48, and 72 h of release.

Initially, previously being exposed to PBS pH 7.4, CBV-PLGA implant (Figure 5-A) and NBV-PLGA (Figure 5-B), and 5.000x magnification micrographs in Figures 6-A and 6-B demonstrate a smooth and homogeneous surface indicating that the hot molding process does not cause macroscopic changes or abnormalities on the device's surface. That can be attributed to the satisfactory mechanical properties of PLGA, as discussed by other authors (Mir *et al.*, 2017).

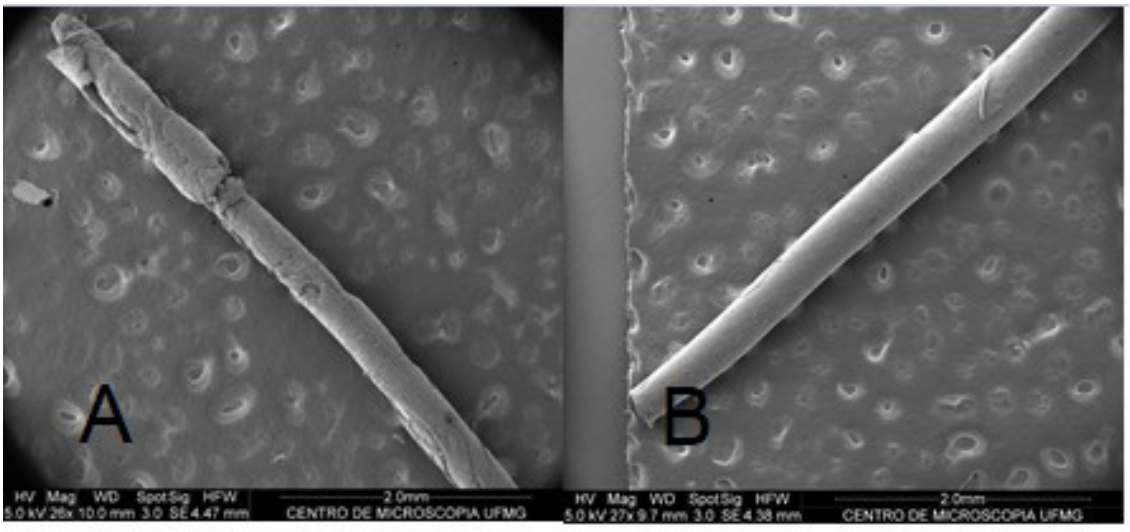

FIGURE 5 - Micrographs of CBV-PLGA (A) and NBV-PLGA (B) implants at 26x magnification. The homogeneous surface without fractures of the implants is evidenced.

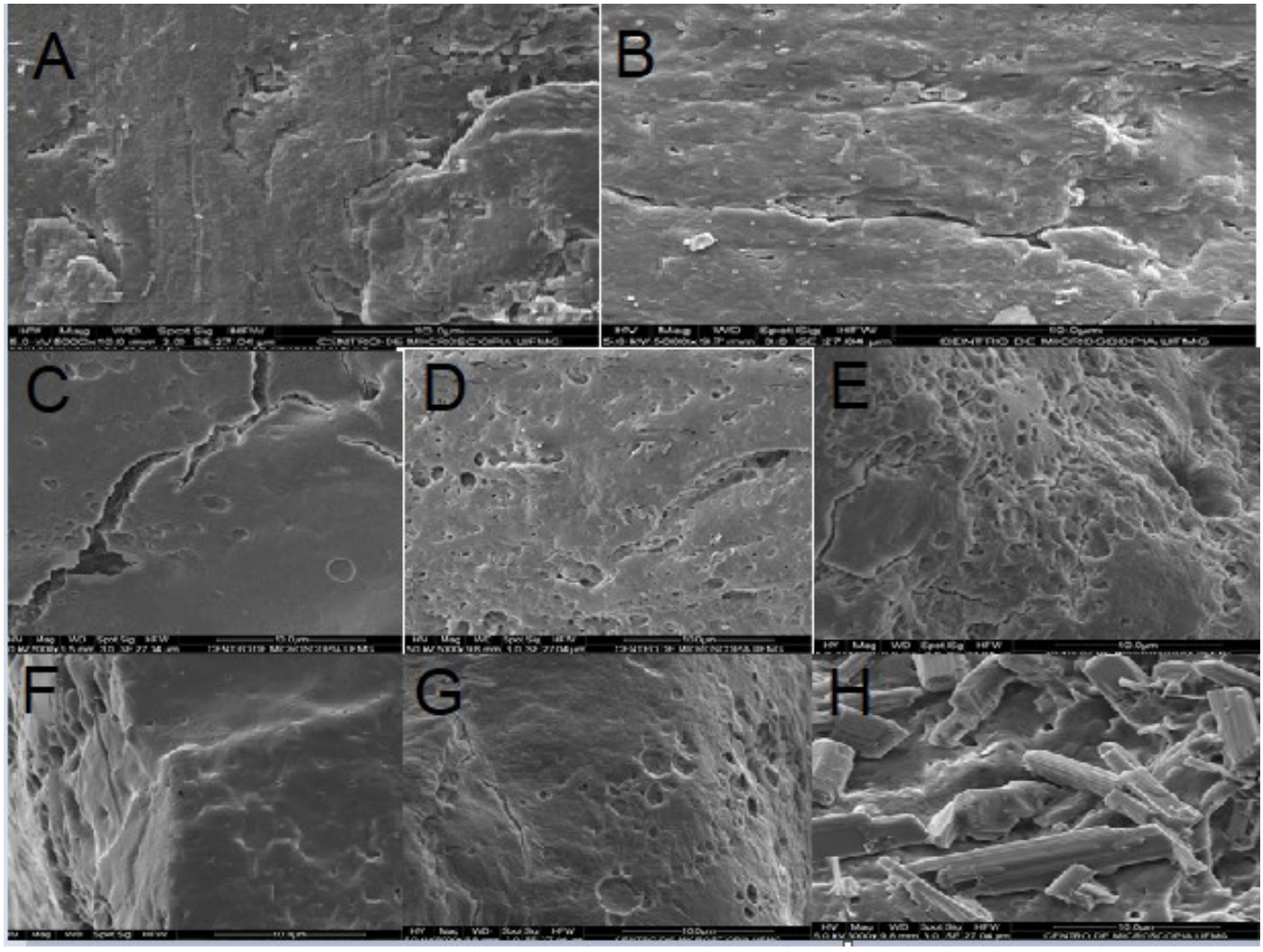

FIGURE 6 - Micrographs of the implants before the *in vitro* test for CBV-PLGA (A) and NBV-PLGA (A) at 5000x magnification. Micrographs during the 24h *in vitro* release test: CBV-PLGA (C), NBV-PLGA (F); 48 h: CBV-PLGA (D), NBV-PLGA (G); and 72h: CBV-PLGA (E), NBV-PLGA (H). Pore formation and polymer erosion can be seen.

After 24 hours exposed to phosphate buffer, it is possible to notice the appearance of some channels on the surface of CBV implants (Figure 6-C) and for NBV (Figure 6-F). The phenomenon intensifies during the 48-hour period (Figures 6-D and 6-G).

Finally, at the end of the period, the number of pores in CBV implants (Figure 6-E) is quite expressive, whereas for NBV implants (Figure 6-H), there is also the appearance of crystals, indicating that the surface layer of the implant was disintegrated, and drug particles were exposed to the medium. The difference between drug crystals' appearance for the NBV-PLGA could be related to enantiomeric proportions since drug release was higher after 72 hours, according to the *in vitro* release test. However, further studies are necessary to figure out such differences.

PLGA-containing formulations include numerous potential drug release mechanisms, including diffusion through the polymer, osmotic flow, diffusion via pores, and polymeric erosion, which are regulated by several physicochemical variables, including formulation composition, release media, size, and shape, among others (Fredenberg *et al.*, 2011; Lopes *et al.*, 2018). The present results suggest that the release of the two types of inserts (CBV and NBV) exhibited the same general release process, commencing with superficial pores development and progressing to insert surface erosion.

CONCLUSION

The present study demonstrated that the 25%:75% drug/polymer ratio is the most suitable for implant molding, ensuring a relatively straightforward process with mechanically resistant implants. Furthermore, the physicochemical findings indicate that drugs and polymers are compatible, no chemical incompatibilities were found, and no degradation products.

The implants were able to release the drugs for 30 days, and NBV-PLGA had a higher release rate than CBV-PLGA, a phenomenon that needs further study to identify the reason. Moreover, the implant's release mechanism was related to the formation of pores and subsequent erosion, showing its biodegradation capacity. In conclusion, the developed implants pave the way for new extended-release systems for local anesthetics.

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